Metastatic acral lentiginous melanoma in a tertiary referral center in Switzerland: a systematic analysis

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OPEN

Metastatic acral lentiginous melanoma in a tertiary referral center in Switzerland: a systematic analysis

Esther M. Häfliger[a,b], Egle Ramelyte[a], Joanna Mangana[a], Michael Kunz[a], Dmitry V. Kazakov[a,c], Reinhard Dummer[a] and Phil F. Cheng[a]

Acral lentiginous melanoma (ALM) is a unique histopathological subtype of melanoma with a poorer prognosis than other cutaneous melanomas. This study aims to evaluate the clinicopathological characteristics, metastatic pattern, prognostic factors, response to systemic therapy, and overall survival (OS) of ALM in a White population. This is a retrospective study of patients who were diagnosed and/or treated for ALM at the Department of Dermatology of the University Hospital Zurich, Switzerland, from January 2005 to December 2015. Overall, 172 patients with histologically confirmed ALM were included in the study. In univariate Cox regression, Breslow thickness ($P < 0.001$), age ($P = 0.003$), status of sentinel lymph node ($P = 0.005$), and ulceration ($P = 0.008$) were identified as significant prognostic factors for OS in ALM. In multivariate analysis, only Breslow thickness ($P = 0.0003$) showed statistical significance. The median OS (mOS) was 155.7 months in the entire cohort ($n = 172$) and 11.2 months for stage IV patients ($n = 36$), irrespective of treatment. When first treatment was considered ($n = 35$), mOS for stage IV patients was 8.9, 16.6, 21.7, and 3.7 months, for patients who had received chemotherapy (ChT) ($n = 17$), immunotherapy ($n = 9$), targeted therapy (TT) ($n = 3$), and no therapy ($n = 6$), respectively. The overall response rate was 44% (7/16 patients) to ChT, 100% to TT (3/3), and 25% to ipilimumab (2/8). In our study, Breslow thickness represents the best prognostic factor for OS. In stage IV ALM patients treated with either immunotherapy or TT, there is a trend for extended mOS compared with ChT. *Melanoma Res* **28:442–450 Copyright © 2018 The Author(s). Published by Wolters Kluwer Health, Inc.**

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Keywords: acral lentiginous melanoma, metastatic spread, prognostic factors, sentinel lymph node biopsy, survival, systemic therapy

[a]Department of Dermatology, University Hospital Zurich, Zurich, [b]Department of Internal Medicine, Zuger Kantonsspital, Baar, Switzerland and [c]Department of Pathology, Medical Faculty in Pilsen, Charles University in Prague, Pilsen, Czech Republic

Correspondence to Reinhard Dummer, MD, Department of Dermatology, University Hospital Zurich, Gloriastrasse 31, 8091 Zurich, Switzerland
Tel: +41 442 552 507; fax: +41 442 558 988; e-mail: reinhard.dummer@usz.ch

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Introduction

Acral lentiginous melanoma (ALM) is a unique subtype of melanoma that affects the glabrous skin of the palms and soles, including the nail apparatus [1,2].

Histologically, it shows a proliferation of atypical melanocytes along the dermoepidermal junction, extending into deeper structures in cases of invasive disease.

ALM is rare in the White population and accounts for 1–3% of all melanomas in Switzerland [2]; however, it is the most common melanoma subtype found in dark-skinned and Asian populations [3]. In contrast to cutaneous melanomas (CM), ultraviolet (UV) radiation does not seem to play a major pathogenetic role in ALM [4]; however, some groups considered mechanical stress to be one of the main factors that increase the formation of melanomas on the plantar surface and pressure points [5,6]. There seem to be distinct patterns of genetic alterations within melanoma subtypes, including different chromosomal aberrations and frequency of mutations of specific genes, suggesting that distinct tumor subtypes develop through different molecular pathways. One of the characteristics of ALM is its unique genomic instability, which results in numerous focused gene amplifications and deletions, which can already be detected at early stages of the disease [1,4]. Activating *BRAF* and *NRAS* mutations are the most common genetic aberrations in cutaneous melanoma, but are detected only in 13–20% [7,8] and 12–25% [8,9] of ALMs, respectively. In contrast, although rare in CM (1.7–14%) [10,11], *KIT* has been reported to be the most commonly mutated gene in ALM, affecting 5–36% of tumors [1,11]. Determination of the genetic background has implications for melanoma therapy as *KIT* mutated tumors show response to therapy with tyrosine kinase inhibitors Nilotinib [12] and Imatinib [11].

Because of the low incidence of ALM in the White population, only a few studies on this melanoma subtype exist to date [13–16]. Despite its rarity, it is an especially important subtype as it seems to lead to a poorer prognosis compared with CM [17,18].

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We present one of the largest cohorts of ALM from a single referral center in Switzerland. The aim of our study was to analyze the clinicopathological characteristics, prognostic factors, response to systemic therapy, and overall survival (OS) of patients with ALM.

Patients and methods

Patient selection and data acquisition

We carried out a single-center retrospective cohort study of all patients who had been diagnosed and/or treated for ALM at the Department of Dermatology of the University Hospital Zurich, Switzerland, from January 2005 to December 2015.

Patients were selected from our DermaPro database system (ifms GmbH, Saarbrücken, Germany) using the keywords 'acral, acral lentiginous, ALM'. Demographic and clinical information was obtained from electronic medical records; missing information was collected through phone interviews with the attending dermatologist or the patient himself/herself.

The primary tumor specimens were retrieved and subjected to re-examination by an experienced dermatopathologist (R.D. or D.K.). The diagnosis of ALM, location (ALM of palmoplantar glabrous skin vs. ALM of nail apparatus), and tumor characteristics such as Breslow thickness and ulceration status were re-evaluated. If the primary excision was performed in an external pathology institute, the slides were ordered for re-evaluation. Only patients with available primary tumor specimens and with a histologically confirmed melanoma arising from the glabrous skin of palmoplantar areas or from the nail apparatus were included in the study.

The demographical and clinicopathological parameters of eligible patients, including age, sex, mutational status, and primary tumor characteristics, were obtained.

The electronic medical records were also reviewed for status of sentinel lymph node biopsy (SLNB) and data on the metastatic pattern. Lymphatic route was defined as developing metastases first confined to the drainage area of regional lymph nodes (corresponding to satellite/in-transit metastases, micrometastases in the SLNB, or clinically recognizable macrometastases in regional lymph nodes), followed by the development of distant metastases [19]. Hematogenous spread was defined as developing distant organ metastases, without previous metastatic involvement of regional lymph nodes. Stage IV patients were divided into four groups according to the first treatment received: chemotherapy (ChT), immunotherapy (IT), targeted therapy (TT), and no systemic therapy.

OS of the entire cohort was calculated from the date of first diagnosis until the date of death or last follow-up. OS of metastatic patients was calculated from the date of first distant metastasis until the date of death or last follow-up. Progression-free survival (PFS) was calculated from treatment initiation until progression or last follow-up. The overall response rate (ORR) was defined as the proportion of patients who showed a partial or a complete response to therapy at the 3-month follow-up by PET-CT.

Informed consent for tissue storage including a retrospective analysis with collection of clinical, laboratory, and histological information was approved by the local ethics committee (KEK-ZH-Nr. 647, 800) and signed by the study participants.

Statistical analysis

Survival analysis was carried out using the log-rank test. Relevant clinical parameters (age, Breslow thickness, sex, etc.) were evaluated by univariate and multivariate Cox regression. The χ^2-test was used to compare the clinical factors between the nonmetastatic and metastatic ALM patients. A P value of less than 0.05 was considered statistically significant.

Results

Patient characteristics

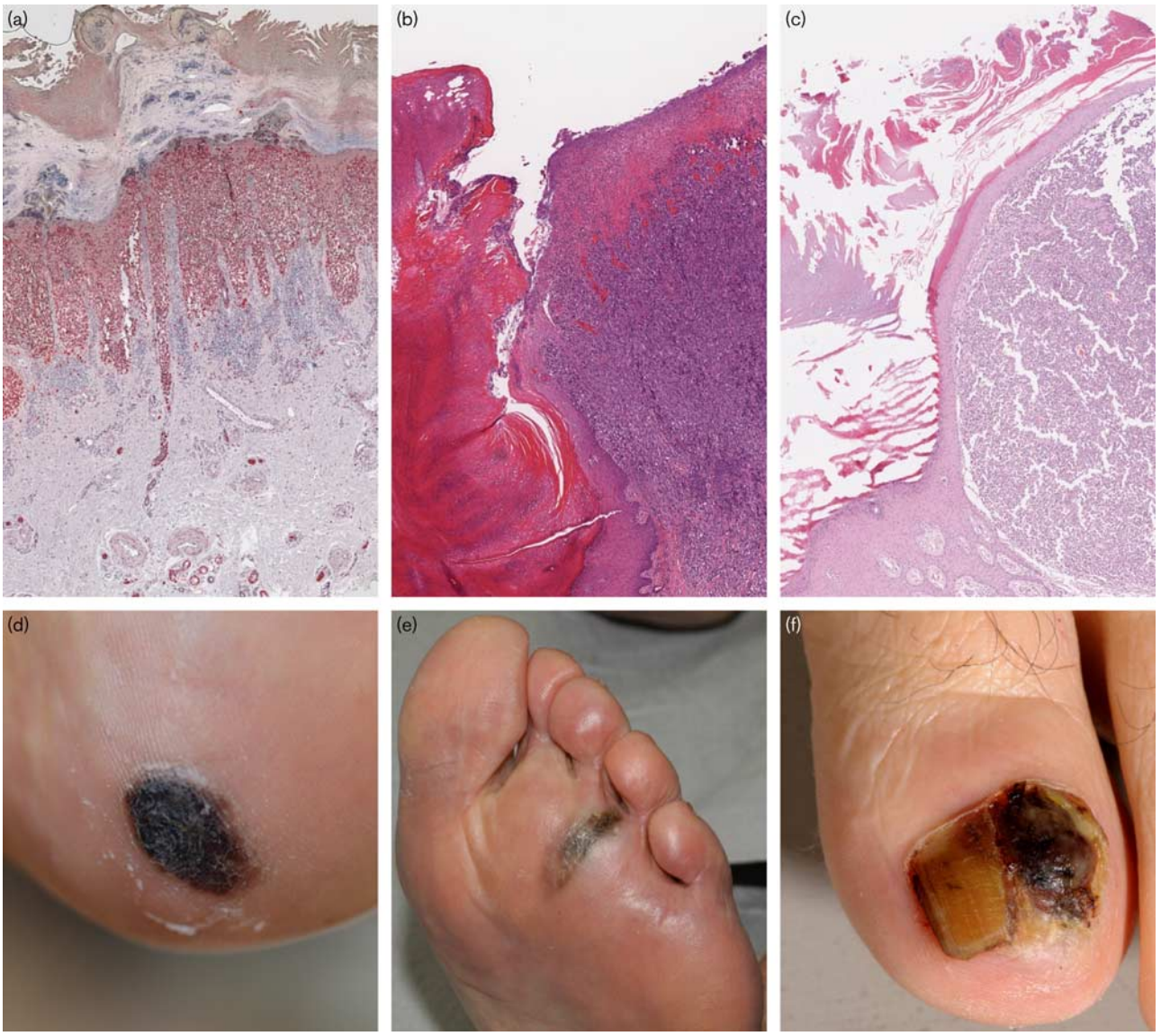
A total of 172 patients fulfilled the inclusion criteria and were included for analysis (Supplementary Fig., Supplemental digital content 1, *http://links.lww.com/MR/A43*, for a schematic display of the patient selection process). For clinical and histological images of ALMs of our series, see Fig. 1. Of all the patients, 96 (55.8%) were women and 76 (44.2%) were men. The median age at first diagnosis was 65 years (range: 27–93 years). The demographical and clinicopathological characteristics of the patients are presented in Table 1. The tumor originated from the glabrous skin of palms and soles in 109 (63.4%) cases and from the nail apparatus in 59 (34.3%) cases. In four cases, the pathologist could not distinguish between glabrous skin and the nail apparatus. Ulceration was present in 53 (42.7%) cases. There were nine (36%) of 25 patients with the *NRAS* mutation, five (23.8%) of 21 patients with the *KIT* mutation, and six (16.2%) of 37 patients with the *BRAF* mutation. Mutation analysis was not carried out in all patients. Most of the tumors were located on the lower extremities [130/172 (75.6%)]. The heel was the most common location [36/130 (27.7%)], followed by a subungual location [26/130 (20%)], forefoot, and midfoot [22/130 (16.9%) each]. Of the tumors occurring on the upper extremities, three-quarters [32/42 (76.2%)] were subungual. For a graphical representation of tumor location, see Fig. 2 (see Supplementary Table, Supplemental digital content 2, *http://links.lww.com/MR/A44*, which shows details on the location of melanomas).

SLNB was performed in 90 of 154 patients with pathologic stage of at least pT1 [90/154 (58.4%)] and was positive in 28 (30.1%) of these patients (Table 1).

Metastatic spread

At first diagnosis, a quarter of the patients with pathologic stage of at least pT1 [36/154 (23.4%)] had metastatic ALM, three of whom had distant organ metastases [AJCC stage IV, 3/36 (8.3%)]. However, by the time of

Fig. 1



Clinical and histological images of five acral lentiginous melanomas (ALMs) of our series. Images (c) and (f) are from the same patient. The rest of the images each stems from a different patient. (a) A nonulcerated ALM of the heel with Breslow 0.7 mm. A lentiginous growth pattern, in which the melanocytes are arranged as solitary units along the basilar epidermis, and the typical propensity of ALM to involve sweat glands can be seen. The thick stratum corneum is a characteristic of plantar location. (b) An ulcerated ALM with Breslow 10 mm of the forefoot. (c, f) An ulcerated subungual melanoma of the hallux with Breslow 3.5 mm. (d) An ALM occurring on the heel. (e) An ALM located on the forefoot.

the last follow-up, the percentage of metastatic disease had increased to 43.5% (67/154). Of the patients with metastatic ALM at the last follow-up, 40 had distant organ metastases: of the 40 patients, 30 (75%) presented with pulmonary metastases, 25 (62.5%) presented with hepatic metastases, 22 (55%) presented with bone metastases, 18 (45%) presented with metastases in other visceral organs, and 12 (30%) presented with cerebral metastases.

Sixty-three (94%) of 67 patients showed a melanoma metastasizing by the lymphatic route, whereas only one (1.5%) of the 67 patients showed hematogenous spread. In three cases, the metastatic route could not be assessed because no SLNB was performed and patients showed distant organ metastases as the first manifestation of metastatic disease. Details of the metastatic pattern are shown in Table 2.

Treatment characteristics

A total of 35 stage IV patients were analyzed according to the first systemic treatment. Seventeen patients received ChT, nine patients received IT, three patients received

Table 1 Patient demographical and clinicopathological characteristics

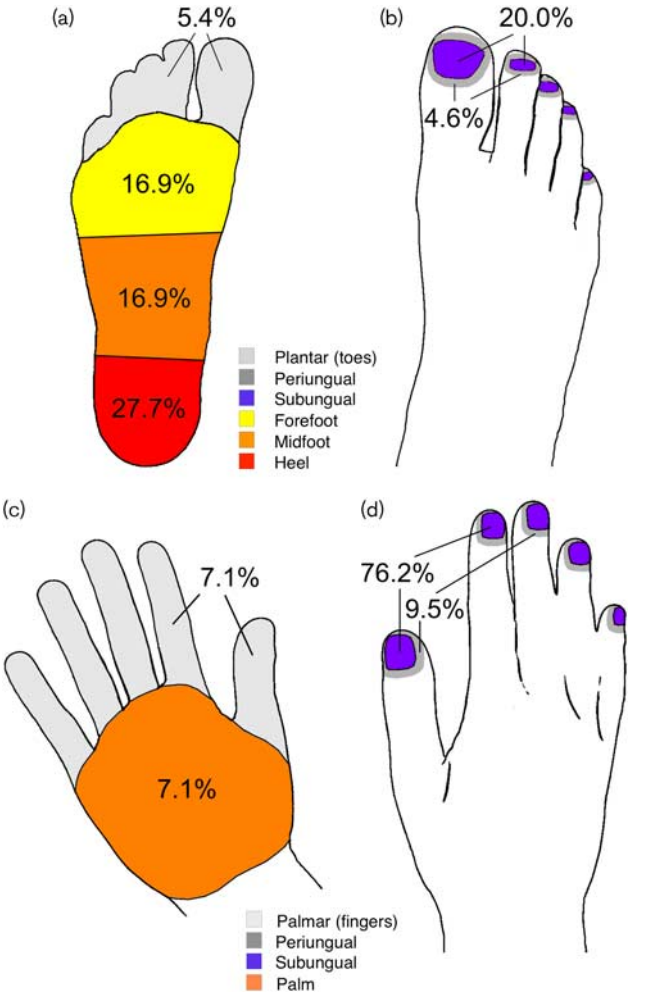
	Nonmetastatic ($n=105$) [n (%)]	Metastatic[a] ($n=67$) [n (%)]
Sex		
Male	42 (40)	34 (50.8)
Female	63 (60)	33 (49.3)
Age (years)	65 (29–86)	65 (27–93)
Origin		
Glabrous skin	62 (59)	47 (70.1)
Nail apparatus	43 (41)	16 (23.9)
Unknown	0 (0)	4 (6)
Location		
Lower extremities	77 (73.3)	53 (79.1)
Upper extremities	28 (26.7)	14 (20.9)
Breslow (mm)	1.8 (0.2–15)	4.2 (0.5–15)
Breslow index (mm) [20]		
In situ	18 (17.1)	0 (0)
0.1–1.0	33 (31.4)	5 (7.5)
1.01–2.0	27 (25.7)	7 (10.5)
2.01–4.0	22 (21)	27 (40.3)
>4.0	4 (3.8)	25 (37.3)
Unknown	1 (1)	3 (4.5)
Ulceration		
Yes	20 (19.1)	33 (49.3)
No	45 (42.9)	26 (38.8)
Unknown	22 (21)	8 (11.9)
Not applicable	18 (17.1)	0 (0)
Stage at first diagnosis [20]		
I	63 (60)	4 (6)
II	37 (35.2)	24 (35.8)
III	0 (0)	33 (49.3)
IV	0 (0)	3 (4.5)
Unknown (stage I or II)	5 (4.8)	3 (4.5)
Mutational status		
BRAF status		
Mutated (V600E, D594N)	0 (0)	6 (9)
Wild type	0 (0)	31 (46.3)
Unknown	105 (100)	30 (44.8)
NRAS status		
Mutated (G12, G13, Q61)	0 (0)	9 (13.4)
Wild type	0 (0)	16 (23.9)
Unknown	105 (100)	42 (62.7)
KIT status		
Mutated (Exon 9, 11, 13, 17, 18)	0 (0)	5 (7.5)
Wild type	0 (0)	16 (23.9)
Unknown	105 (100)	46 (68.7)
SLNB		
T1–T4 ($n=154$)[b]		
Positive	0 (0)	28 (41.8)
Negative	47 (54.0)	15 (22.4)
Not performed	40 (46.0)	24 (35.8)

Age is reported in years as median age and range.
Breslow thickness is reported in mm as mean Breslow and range. All other variables are reported in n (%).
[a]At the time of the last follow-up.
[b]Patients with melanoma *in situ* were excluded.

TT, and six patients did not receive any systemic therapy (Table 3). One patient was excluded from this analysis because he was treated with dacarbazine/adeno-interleukin-2 as the first therapy.

Four (24%) of 17 patients received ChT as the first-line and second-line treatment, whereas for eight (47%) of 17 patients, the therapy was switched to IT or TT. Out of 22 patients, who received IT or TT as the first systemic therapy, eight (27%) were switched to another IT or TT as

Fig. 2



Graphical representation of tumor location. (a–b) Percentages refer to the total of melanomas of the lower extremities. The total is not 100%, because the exact location of 8.5% of tumors is unknown. (c–d) Percentages refer to the total of melanomas of the upper extremities.

the second-line treatment, whereas eight (27%) patients were switched to ChT. Overall, 13 patients received more than two systemic treatments. (see Supplementary Table, Supplemental digital content 3, *http://links.lww.com/MR/A45*, for details on systemic therapy).

ORR was 44% for ChT (7/16), 100% for TT (3/3), and 22% for any IT (2/9) (Table 3). Eight of the nine patients treated with IT received ipilimumab. ORR to ipilimumab first-line treatment in our cohort was 25% (2/8) (see Supplementary Table, Supplemental digital content 4, *http://links.lww.com/MR/A46*, for details of response to first systemic therapy).

Survival data

By the time of the last data collection in September 2016, 108 (62.8%) patients were still alive, 51 (29.7%) patients had died, and 13 patients were lost to follow-up. The median follow-up duration was 49 months (range: 0.1–260.1 months).

Table 2 Clinical course and metastatic pattern of 67 patients

Stage (AJCC) [20]	*n* (%) (*N* = 67)	Location of metastases	*n* (*N* = 40)	Number of affected organs	*n* (*N* = 40)
		At the time of first diagnosis			
I	4 (6)	Lung	3	1 organ	3
II	24 (35.8)	Lung, liver, bone, adrenal	1	2–3 different organs	0
III	33 (49.3)			≥ 4 different organs	1
IV	3 (4.5)				
Unknown	3 (4.5)				
		At time of the last follow-up			
III	26 (38.8)	Lung	30 (75)	1 organ	8 (20)
IV	41 (61.2)	Liver	25 (62.5)	2–3 different organs	18 (45)
M1a	1 (2.4)	Bone	22 (55)	≥ 4 different organs	14 (35)
M1b or M1c	40 (97.6)	Brain	12 (30)		
		Other visceral[a]	18 (45)		
Route of metastasizing					
Lymphatic	63 (94)				
Only lymph nodes	30 (47.6)				
Lymph nodes and satellite[b]	28 (44.4)				
Only satellite[b]	5 (7.9)				
Hematogenous	1 (1.5)				
Unknown	3 (4.5)				

Variables are reported in *n* (%). *N* = 67 represents the total of patients with metastatic disease at the time of last follow-up. *N* = 40 represents the total of patients with distant organ metastases at the time of last follow-up.
[a]Adrenal gland, kidney, spleen, pancreas, gallbladder, urinary blatter, intestine, peritoneal carcinomatosis, stomach, heart, thyroid gland, and palatine tonsil.
[b]Satellite or in-transit metastases.

Table 3 Characteristics of the first systemic treatment, overall response rate, median PFS, and median OS

	Stage IV [20][a]	ORR (%)	Median PFS (months)	Median OS (months)
First systemic treatment (*n* = 35)				
ChT	17 (48.6)	44	2.1	8.9
IT	9 (25.7)	22	2.1	16.6
TT	3 (8.6)	100	11.4	21.7
None	6 (17.1)	–	–	3.7
Ipilimumab as the first-line treatment (*n* = 8)	–	25	2.1	21

Variables are reported in *n* (%).
Chemotherapy included dacarbazine, temozolamide, avastin, vinorelbine + cisplatin (VP), taxol, and depocyte. Immunotherapy included ipilimumab, pembrolizumab and one patient with tremelimumab.
Targeted therapy included BRAF-inhibitors (vemurafenib), MEK-inhibitors (trametinib, selumetinib), BRAF/MEK-inhibitors (dabrafenib + trametinib), multikinase inhibitors (imatinib, sorafenib), and tyrosine kinase inhibitors (nilotinib, pazopanib). For analysis of the first systemic treatment, 1 patient was excluded because he had received dacarbazine/adeno-IL-2 as the first treatment.
ChT, chemotherapy; IT, immunotherapy; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TT, targeted therapy.
[a]Stage refers to beginning of systemic therapy.

The median OS (mOS) was 155.7 months in the entire cohort and 11.2 months for stage IV patients, irrespective of treatment (Fig. 3a and b).

The 5-year OS was 45.2% (14/31) for stage III patients and 5.6% (2/36) for stage IV patients (Fig. 3b). The 5-year OS for stage I–II patients could not be calculated, mainly because of the very short follow-up period.

The median PFS for the first treatment was 2.1 months for ChT (*n* = 17), 2.1 months for IT (*n* = 9), and 11.4 months for TT (*n* = 3) (Table 3 and Fig. 3c). When the first treatment was considered, mOS for stage IV patients was 8.9, 16.6, 21.7, and 3.7 months, for patients who received ChT, IT, TT, and no therapy (*n* = 6), respectively (Table 3 and Fig. 3d). We compared mOS of ChT versus IT and of ChT versus TT and observed a trend toward longer mOS in stage IV ALM patients treated with either IT or TT compared with ChT ($P = 0.057$ for ChT vs. IT, $P = 0.056$ for ChT vs. TT).

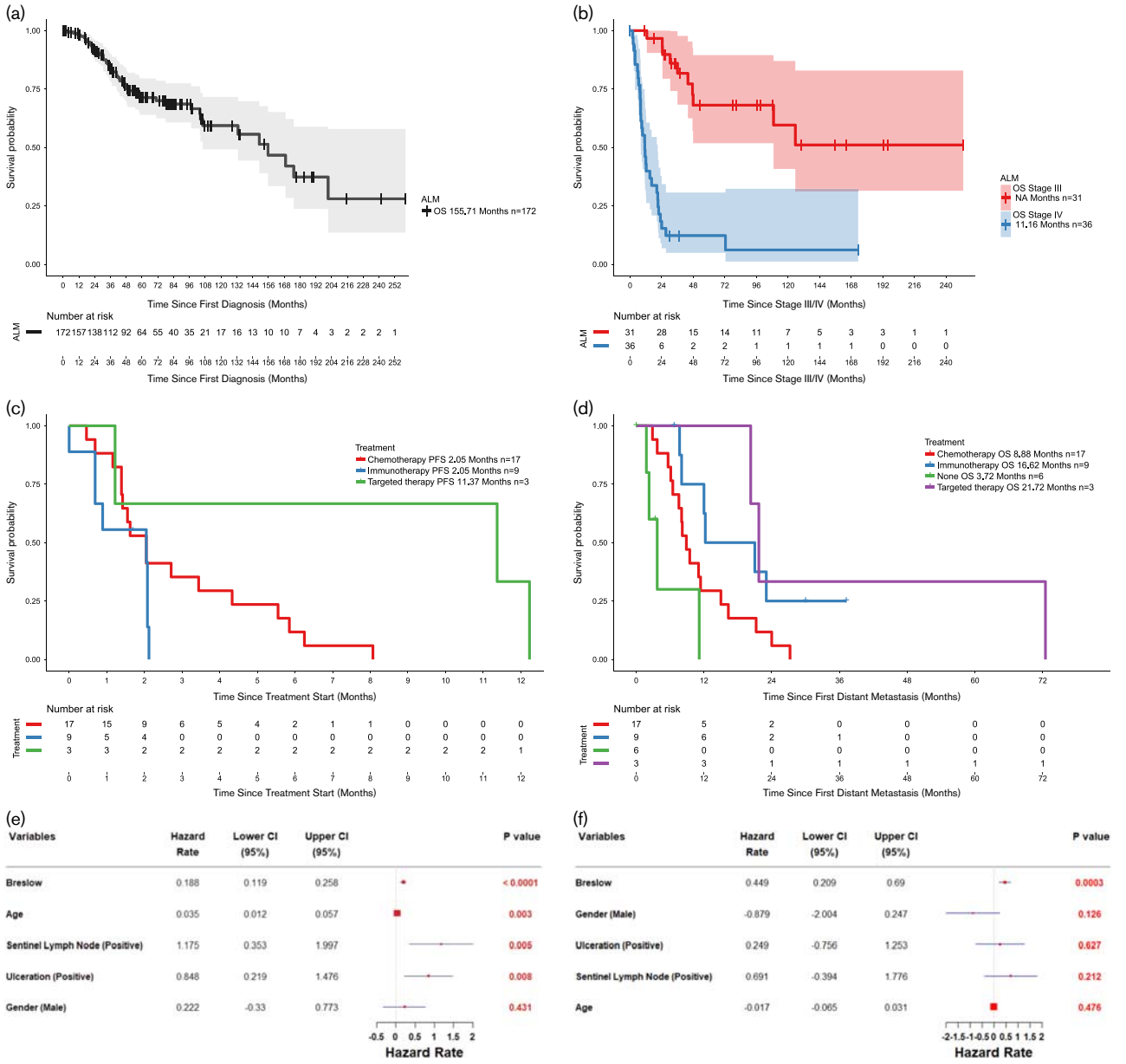
Prognostic factors for overall survival

In univariate Cox regression, Breslow thickness ($P < 0.001$), age ($P = 0.003$), status of sentinel lymph node ($P = 0.005$), and ulceration ($P = 0.008$) were identified as significant prognostic factors for OS in ALM (Fig. 3e). However, only Breslow thickness was a significant prognostic factor for OS ($P = 0.0003$) in multivariate Cox regression. Sex ($P = 0.431$) failed to show statistical significance in both univariate and multivariate Cox regression (Fig. 3f).

Prognostic factors for metastatic disease

Patients with metastatic disease at the time of the last follow-up were more likely to have had ulceration ($P = 0.008$) and pathologic stage of more than pT2 ($P < 0.0001$) at first diagnosis. Almost 15 (25%) of the 65 patients with negative SLNB developed metastatic disease. Subdivided by pathologic tumor stage, five of six patients with pT4 and nine of 27 patients with pT3 eventually developed metastatic disease, despite the negative SLNB, whereas only one of 10 patients with pT1 and none of the pT0–T2 patients with negative SLNB developed metastases (see Supplementary Table, Supplemental digital content 5, *http://links.lww.com/MR/A47*, for details on patients in whom SLNB was performed) (see Supplementary Fig., Supplemental digital content 6, *http://links.lww.com/MR/A48*, for OS according to the status of sentinel lymph node).

Fig. 3



(a) Overall survival (OS) of the entire cohort (n = 172) from the date of first diagnosis until death or the last follow-up. (b) OS for stage III patients (n = 31) versus stage IV patients (n = 36). OS of metastatic patients was calculated from the date of first distant metastasis until death or the last follow-up. The 5-year OS was 45.2% (14/31) for stage III and 5.6% (2/36) for stage IV patients. (c) Progression-free survival (PFS) for stage IV patients according to the first received treatment (n = 35): chemotherapy (n = 17) versus immunotherapy (n = 9) versus targeted therapy (n = 3) versus no systemic therapy (n = 6). PFS was calculated from treatment initiation until progression or the last follow-up. (d) OS for stage IV patients according to the first received systemic treatment (n = 35): chemotherapy (n = 17) versus immunotherapy (n = 9) versus targeted therapy (n = 3) versus no systemic therapy (n = 6). OS was calculated from the date of first distant metastasis until death or the last follow-up. (e) In univariate Cox regression, Breslow thickness, age, status of sentinel lymph node, and ulceration were identified as significant prognostic factors for OS in acral lentiginous melanoma (ALM). (f) In multivariate analysis, only Breslow thickness showed statistical significance. A P value of less than 0.05 was considered as statistically significant. Crosses indicate censored patients. NA, not applicable because 50% death was not reached; OS, overall survival; PFS, progression free survival.

Discussion

We report a large series of 172 patients with ALM from a single tertiary referral center in Switzerland. In this study, we focus on the clinicopathological characteristics, prognostic factors, response to systemic therapy, and OS of this cohort.

The characteristics of the patient population, examined in this study, are in good agreement with those reported in similar studies. Most tumors occurred in female patients [16,17], and the mean age at first diagnosis was 64.4 years, which is only slightly higher than previously published data, reporting a mean age ranging from 55 to 63 years [16–18].

Recent studies in the Asian population found a higher incidence of ALM at more physically stressed sites such as the heels [5,21], whereas formation of ALM in the arch of the foot was reported to occur more commonly in obese patients [6], known to experience flattening of the foot and formation of new pressure points. These observations, along with our data of White patients, suggest that mechanical stress plays a major pathogenetic role in plantar melanoma; however, a more detailed analysis is needed.

Since the Food and Drug Administration approval of TT with kinase inhibitors and IT with immune checkpoint inhibitors in 2011, genetic testing for potential driver mutations with the prospect of treatments became important. In our cohort, the most frequent mutations were found in *NRAS*, followed by *KIT* and *BRAF* genes. The percentage of *KIT* mutations of our study is in accordance with the data provided by other authors [1,11]; however, we found a relatively high percentage of *NRAS* mutations. This could be because of missing data as a considerable proportion of our patient cohort had been diagnosed and/or treated before the introduction of routine screening for individual mutational profiles.

In the past decade, the role of SLNB as an important prognostic factor for recurrence and OS in CM has been proven. It is nowadays a standard procedure for patients with CM with a Breslow thickness of at least 1.0 mm or at least 0.8 with ulceration and clinically nonpalpable regional lymph nodes [2,22]. However, in noncutaneous melanoma, the value of SLNB remains controversial [23,24]. The literature on the relevance of SLNB in ALM is limited to small cohort studies; however, positive SLNB was identified as the main predictor for recurrence and worse survival in a cohort of 85 ALM patients [15], and in another study, ALM patients with positive SLNB were reported to have a significantly worse 5-year OS (37.5 vs. 84.3%) and 5-year PFS (37.5 vs. 77.9%) compared with patients with negative SLNB [25]. We found positive SLNB to be a prognostic factor for lower OS in univariate Cox analysis; however, almost 25% of the patients with negative SLNB developed metastatic disease. The false-negative predictive value of SLNB for our ALM series is higher than that reported for CM (11–16%) [26,27]. This may in part be explained by the fact that our dataset was incomplete. In fact, SLNB was only performed in 58.4% of patients. Also, most of our SLNBs were not performed at a specialized center; thus, the high quality of histopathological assessment of SLNB [28] might not always have been provided.

Distinct melanoma subtypes show different metastatic patterns [28], with ALM and mucosal melanoma showing a tendency to develop significantly more bone metastases compared with other melanomas. In our cohort of metastatic ALM, bone metastases were found in over a half of the patients. It has been reported that the cytokine tumor growth factor-β plays an important role in antagonizing the development of bone metastases in melanoma and breast cancer [29,30]. Thus, the differences in organ preferences of metastatic spread within distinct melanoma subtypes might derive in part from a different dependence on tumor growth factor-β signaling pathways [28].

Until 2011, ChT with dacarbazine was considered the standard treatment for patients with inoperable or metastatic melanoma and alternatives were limited [31]. It yielded objective response rates of 5–15% in several phase III studies, but failed to show an impact on OS, so that until 2011, the median OS was only 8–10 months with approved therapies for stage IV melanoma [31–35]. In our study, ChT as the first-line treatment showed an ORR of 44% for stage IV ALM, which is higher than previously reported data for CM. However, the mOS of 8.9 months was within the range reported in the literature for CM [32–35]. Fortunately, treatment of metastatic melanoma has changed considerably over the last decade with the development of IT and TT. These new drugs not only show better ORR compared with ChT but also improve OS [36]. Ipilimumab, which blocks cytotoxic T-lymphocyte-associated antigen 4 to augment antitumor T-cell immunity, was the first agent to show a benefit for OS in metastatic melanoma in randomized-controlled phase III trials [19,37,38].

The mOS of patients treated with ipilimumab in our cohort was almost twice as long (21 months) as the reported median OS for patients with CM (11.4 months) [39]. Although the response rate to ipilimumab is only 15% in CM, up to 21% of stage IV patients, independent of previous therapy, achieve remarkable durable remission [19,39]. In our study, two (25%) of eight patients responded to ipilimumab as the first systemic treatment, and one of them showed a durable remission of 37.2 months. Until the time of data collection, this patient did not receive other systemic treatments after ipilimumab and did not show any tumor progression. The considerable difference in the mOS and ORR between our data and the literature might be because of the small number of patients who received ipilimumab as the first treatment in our study ($n=8$). As the clinical outcome of stage IV melanoma patients treated with ipilimumab is not reported separately for the ALM subcategory in the literature, but exclusively for stage IV melanoma patients overall, without differentiation of histological subtype,

this difference could also be explained by different susceptibilities of the various melanoma subtypes to ipilimumab. In our study, we found a trend toward extended mOS in stage IV ALM patients treated with either IT or TT compared with ChT. The lack of statistical significance is likely because of the low number of patients whom we included in treatment analysis.

Teramoto *et al.* [16] analyzed a cohort of 2050 ALMs and suggested that advanced age, ulceration, tumor thickness, and tumor spread at first diagnosis were reliable independent prognostic factors for disease-specific survival, and hence, the present AJCC classification for CM can be considered valid for ALM. In our study, we found Breslow thickness, age, status of sentinel lymph node, and ulceration to be prognostic factors for OS in univariate analysis. The finding of SLNB as a prognostic factor for OS is in line with previously published data [15,25].

ALM seems to be associated with worse prognosis compared with CM. In patients with stage III disease, the 5-year OS was reported to be 61.2 versus 66.1% for ALM and CM, respectively [18]. As for stage IV patients, the 5-year OS was 22.2 versus 25.5%, respectively, for ALM and CM [18]. In our study, the 5-year OS was 45.2% for stage III patients and 5.6% for stage IV patients.

The reasons for the unfavorable prognosis of ALM remain unclear. Because of the hidden location of plantar melanomas and the striking similarity of subungual tumors to hematomas, ALM is often diagnosed in a more advanced tumor stage compared with CM [17–19]. Besides the delayed diagnosis, the lower survival rates found in ALM may also be caused by a different biological tumor behavior [4,11,13,16,18,40,41]. Newly reported prognostic genetic biomarkers in ALM may contribute toward a better prognostication of ALM patients. Amplification of the telomerase reverse transcriptase (*TERT*) gene, and increased levels of β-catenin, lymphoid enhancer-binding protein-1, and heparanase-1 were reported to be associated with poor outcomes in ALM [42,43].

The retrospective setting, the small cohort of metastatic patients, and the diversity of systemic therapies administered to these patients are clear limitations of our study. To our knowledge, this is the largest study reporting the exact location of ALM.

Conclusion

ALM is a unique subtype of melanoma, which is characterized by a poorer prognosis compared with CM. As delayed diagnosis seems to be one of the main causes for poor outcomes in ALM, sensitization of the population to the existence of melanoma on hidden locations such as acral sites or the nail apparatus, and regular skin checks and self-examinations of acral sites may lead to earlier diagnosis and therefore directly improve survival.

Moreover, we found a trend toward extended mOS in stage IV ALM patients treated with either IT or TT compared with ChT. Prospective clinical trials with larger cohorts of stage IV ALM patients are needed to further elucidate the effect of new systemic therapies such as IT and TT on the survival of ALM patients.

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Conflicts of interest

Professor Dummer receives research funding from Novartis, Merck Sharp & Dhome (MSD), Bristol-Myers Squibb (BMS), Roche, and GlaxoSmithKline (GSK), and has an intermittent consultant or advisory board relationship with Novartis, Merck Sharp & Dhome, Bristol-Myers Squibb, Roche, GlaxoSmithKline, and Amgen outside the submitted work. J.M. has temporary consultant or advisory relationships (Merck/Pfizer) and receives travel support from Merck Sharp & Dohme. For the remaining authors, there are no conflicts of interest.

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